Genetics of Mental Disorders. A Guide to Students, Clinicians, and Researchers. Faraone SV, Tsuang MT, Tsuang DW. New York: The Guilford Press; 1999. 272 pp with index. ISBN 1-57230-479-0 (cloth). US$30.

The initial sequencing results and analysis of the human genome were published in February 2001, and the data now available, although preliminary, are of critical importance, given the amount of information potentially held in the DNA sequence regarding evolution, human development, physiology and normal and abnormal brain functions.

In this context, the book *Genetics of Mental Disorders* appears particularly timely, in that it represents a valuable guide to understanding the main issues implicated in the study and treatment of psychiatric disorders from a genetic perspective.

The volume provides a clear and solid basis for an understanding of the genetics of complex traits, from the basic principles of the classical mendelian laws, through the bases of molecular strategies to detect genetic susceptibility, to the nonmendelian patterns of inheritance in psychiatric disorders. Overall, the book has a clinical flavour and constantly refers to the practical clinical applications of information derived from psychiatric genetic studies. Thus, it will be particularly appealing to readers who are not experts in the genetics of complex traits but who want to learn more about this rapidly expanding field. The basic concepts are easily accessible, especially given the concise but substantial glossary, where the meaning of technical terms such as "imprinting," "linkage," "linkage disequilibrium," "phenocopy" and "penetrance" are clearly and effectively explained.

The first 2 chapters introduce the epidemiological bases of psychiatric genetics and the complex factors involved in the study of the heritable nature of psychiatric disorders (including the problem of clinical heterogeneity of psychiatric phenotypes and the complex interaction between genetic and environmental factors in determining their expression). Particularly valuable in this introductory overview is the fact that epidemiological data and information about the complex interactions between genes and environment are addressed from a clinical perspective, with frequent reference to the importance and utility of this information for clinical practice.

The concepts of clinical and etiologic heterogeneity, as well as genetic, biological and clinical dimensions, are clearly discussed in chapter 3. The chapter is enriched with a description of the different approaches suitable for addressing and understanding these issues in both the clinical and the research settings, and it includes a good review of studies on the genetics of schizophrenia, bipolar disorder and attention deficit hyperactivity disorder.

The heterogeneity of the clinical and neurobiological correlates of mental disorders is of particular relevance in psychiatric genetics. In most of the genetic studies on psychiatric disorders performed to date, the phenotype has been defined as the clinical diagnosis. However, the diagnosis, even though structured and validated, is often heterogenous and covers patients with different clinical characteristics, outcomes, biological characteristics and responses to medication. Thus, the definition of more homogenous subphenotypes is likely to be a valid and innovative alternative strategy to deal with the complexity of any psychiatric phenotype. As an example, the consideration of traits that display quantitative variations within a given diagnostic category, instead of (or together with) the diagnosis, has been recognized as a good strategy to take into account the heterogeneity of psychiatric diseases and the complex influence of genetic factors in determining them.

According to a logical sequence, the chapter on causal and clinical heterogeneity in psychiatric disorders is followed by an overview of the available mathematical models to study the mode of inheritance of a given disease. Strategies applicable to both mendelian and nonmendelian diseases are reviewed, together with models of oligogenic and polygenic inheritance, the study of the heritability of quantitative traits, and the genetic concepts of liability and penetrance. Again, the most valuable quality of this section is its simple, clear descriptions of complex mathematical models, with frequent reference to the clinical utility of the information provided. The reader will find suggestions regarding

how to use this information in the clinical setting, together with a solid background to help in answering the most common questions asked by patients and their relatives. This aspect makes the section particularly suitable for readers who are not geneticists, although researchers with some expertise in the field will miss more specific information about epistasis and the new population-based approaches to the study of models of gene–gene interaction.

The human genome shows variability across individuals that may underlie variations in biological function, susceptibility to illness or response to medication. There appear to be 30 000 to 40 000 protein-coding genes in the human genome and more than 1.4 million single-nucleotide polymorphisms. The authors review the basic concepts of the various analytical strategies for molecular genetic data, such as linkage analysis, case–control and family-based association designs. The most widely used and validated family-based association design is now the Transmission Disequilibrium Test (TDT), which the authors discuss extensively. The investigation of an association between a given gene and a given disease by means of the TDT has been considered a particularly useful strategy in identifying genes that may contribute to disease susceptibility, especially when the genes are assumed to be of small effect, as in psychiatric disorders. The TDT has been extended recently to the analysis of quantitative traits and thus appears to hold promise for the study of the genetic basis of clinically relevant phenotypes related to dimensions of psychiatric disorders (e.g., age at onset and severity of symptoms).

The chapter on the clinical application of psychiatric genetics covers the instruments used in clinical interviews for genetic purposes, several aspects of genetic counselling and the implications of genetic assessment for the diagnosis and treatment of psychiatric conditions. As an example, the importance of obtaining a good family history for clarifying the diagnosis of probands in families with atypical phenotypes is discussed, together with "clinical tips" to obtain the most reliable information from interviews and case reports.

The last chapter gives an insightful overview of the future of psychiatric genetics, including a careful discussion of the ethical issues implicated by the extensive use of genetic testing.

Perhaps the most promising application of the new genetic knowledge and the new genetic strategies for decoding the information carried by the human genome is the development of new therapeutic strategies and accurate prediction techniques for complications or adverse events during the course of a given medication treatment of illness. This line of research is called pharmacogenetics. Its main goal consists of identifying the genetic factors responsible for variability in response to medication, which is a critical, but still unsolved, problem in psychiatric care. Armed with information about the genetic makeup of individual patients, we will be able to design new therapeutic compounds that relate directly to specific genetic information and to accurately predict response to medication for each patient. This will lead to a dramatic improvement in the long-term outcome of psychiatric diseases that are often chronically disabling and difficult to treat.

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Central Nervous System Diseases: Innovative Animal Models from Lab to Clinic. Emerich DF, Dean RL 3rd, Sanberg PR, editors. Totowa (NJ): Humana Press; 2000. 512 pp with index. ISBN 0-896-03724-X (cloth). Can$145.

Medical research depends heavily on the use of nonhuman models, particularly in preclinical evaluations of interventions. However, the appropriate choice of animal model is not always obvious; it depends on the disorder of interest and on the appropriateness of the particular species for modelling that disorder. The validity of any given model is established by its similarity to the disorder, its similarity in underlying mechanisms and its ability to predict the effectiveness of interventions. Yet too often, model selection is based on practical considerations, independent of validity.

Central Nervous System Diseases: Innovative Animal Models from Lab to Clinic focuses on the development and utility of animal models for particular types of central nervous system (CNS) disorders. The focus is on disorders associated with obvious brain abnormalities. CNS disorders such as depression, which are not associated with obvious neurodegeneration, are not covered. Also lacking is coverage of disorders associated with infec-

tious agents, such as human immunodeficiency virus. The editors' stated goal is to provide practical information. To this end, the authors were encouraged to critically examine the various models and to discuss both their advantages and disadvantages.

Four of the 5 sections address specific types of neurodegenerative disorders: aging and Alzheimer's disease; Parkinson's disease; Huntington's disease; and traumatic brain injury, stroke and hypertensive cerebrovascular disease. Section 5 looks at examples of animal models leading to clinical trials. Each of the first 4 sections starts with an article on behavioural analysis, which provides a useful overview of the types of behavioural techniques used in developing particular animal models.

In section 1, on aging and Alzheimer's disease, all but 1 of the 7 chapters deal with rodent models, which is unfortunate, given that the types of cognitive deficits seen in aged rodents are only questionably comparable to those associated with either aging or Alzheimer's disease. Similarly, rodents do not experience the neuroanatomic abnormalities seen in the human brain (e.g., neurotic plaques and neurofibrillary tangles). The problematic nature of the behavioural and neuroanatomic correlates warrants a greater focus on more advanced species. One chapter discusses age-related cognitive decline in the rhesus monkey. The authors point out that aged monkeys can be used to model human cognitive aging, but not Alzheimer's disease. If a primate cannot adequately model Alzheimer's disease, how likely is it that the rat will?

Section 2 deals with Parkinson's disease, and again, all but 1 of the 6 chapters focuses on rodent models. The clinical relevance of the movement disorders seen in rodent models is questionable. Rotometry, the most commonly used rodent measure, does not model any symptoms of Parkinson's disease. The models focus only on motor deficits, omitting modelling of the accompanying cognitive changes.

Section 3, which deals with Huntington's disease, has 5 chapters. Several rodent models described in this section are based on damage to the striatum. None of these provide valid behavioural correlates, since rats do not exhibit choreiform movements. Furthermore, the rat striatum, unlike that of the primate, does not have a distinct caudate nucleus and putamen. The motor disorders of Huntington's disease are better modelled by primates with damage to the striatum, which can be produced by either lesions or chronic treatment with 3-nitropropionic acid, a poison that disrupts cellular metabolism.

Section 4 deals with traumatic brain injury, stroke and hypertension. These disorders are fundamentally different from those discussed in the first 3 sections because of the broader range of behavioural and anatomic deficits seen clinically. Animal models are particularly useful in helping to establish how mechanical injury or stroke produces brain damage and how this damage can be prevented and treated.

The last section of the book discusses instances of animal models with clinical applications. These examples are probably most useful in showing how far we still have to go before animal models can reliably lead to therapeutics. Thus far, neither neural grafting nor gene therapy has been convincingly shown to be clinically effective for neurodegenerative disorders.

Overall, this is a useful volume for those involved in animal research on neurodegenerative disorders because it provides insight into the process of model development and selection. Such insight is particularly important for the development of interventions for CNS disorders. The articles are generally well written, and some of the models described are promising. But the selection of models is, of necessity, limited, with too much attention devoted to rodent models. Equally problematic is the failure in many instances to critically assess the validity of the model. The limited number of models discussed restricts the usefulness of the volume as a reference source.

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